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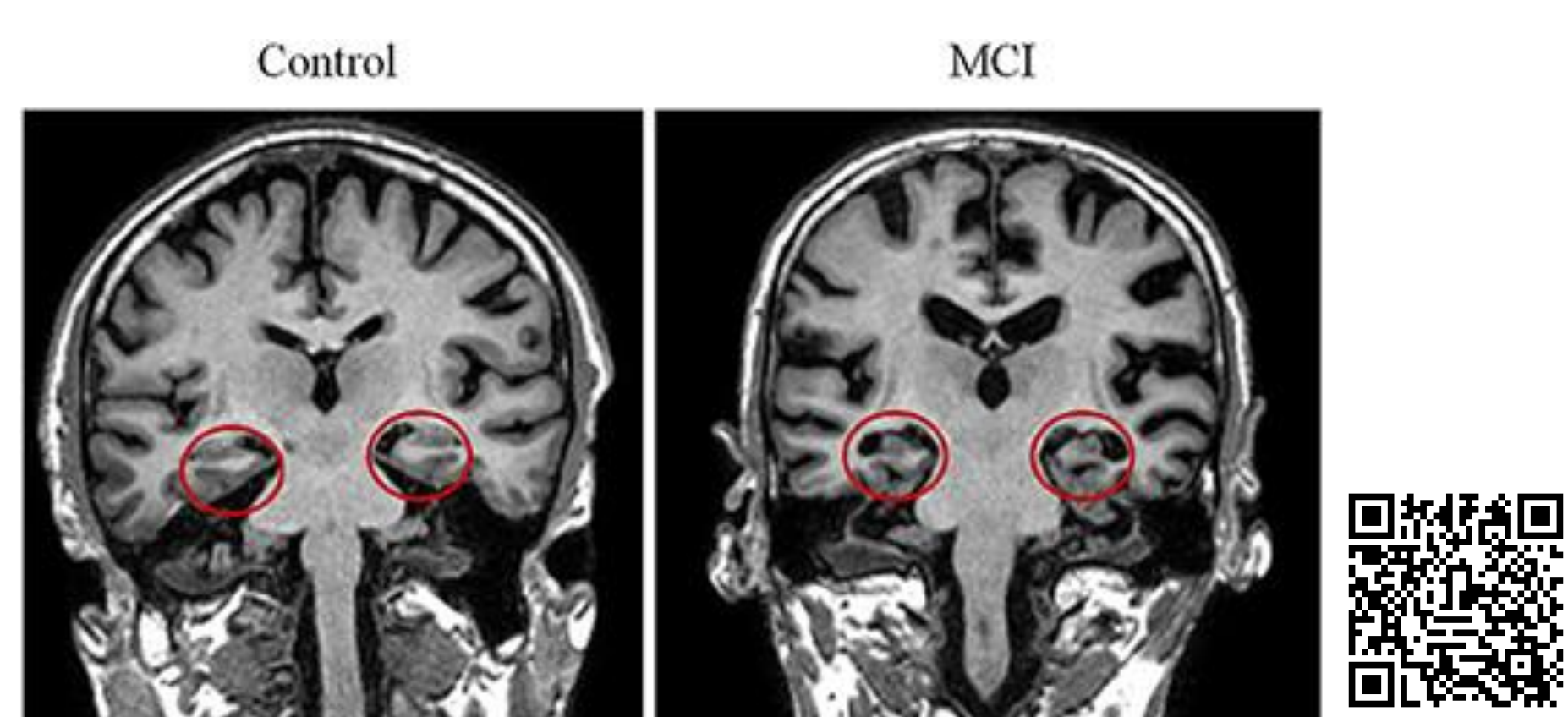
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## Background

- Disease-modifying/preventative treatments for Alzheimer disease (AD) and Parkinson disease (PD) are expected to be most effective at early disease stages.
- Early stage selection of the right subjects is challenging due to pathophysiological uncertainty or patient heterogeneity.
- Here, we present pharmacometric analyses examining the enrichment utility of intracranial-adjusted-hippocampal volume (ICV-HV\*) for mild cognitive impairment (MCI), and dopamine transporter (DAT\*\*) neuroimaging for early stage PD trials, respectively (Figure 1).

### (A) Hippocampal Volume (ICV-HV) Neuroimaging



### (B) Dopamine Transporter (DAT) Neuroimaging



**Figure 1. Candidate enrichment biomarkers in (A) MCI, and (B) PD.**

ICV-HV is determined by magnetic resonance imaging (MRI); DAT deficit is determined by single-photon emission computed tomography (SPECT).

## Objectives

Obtain regulatory qualification of enrichment biomarkers that select subjects most likely to exhibit clinically relevant disease progression.

\* Results for ICV-HV in MCI are preliminary and subject to modifications.

\*\* Results for DAT in early stage PD have been published at Ref. 1.

### References:

- (1) Conrado DJ *et al.* Clin Transl Sci. (2017). [Epub ahead of print]
- (2) The Parkinson Progression Marker Initiative (PPMI). Prog. Neurobiol. 95, 629–635 (2011).
- (2) Parkinson Study Group PRECEPT Investigators. Neurology 69, 1480–1490 (2007).
- (3) Conrado DJ, Denney WS, Chen D, Ito K. J Pharmacokinet Pharmacodyn. 41(6):581-98 (2014).

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## Methods

- **Data:** C-Path assembled subject-level, longitudinal, CDISC-standardized datasets.
  - *Early stage PD:* data came from the Parkinson's Disease Progression Markers Initiative [PPMI (Ref. 2)] observational study and from the Parkinson Research Examination of CEP-1347 trial [PRECEPT (Ref. 3)].
  - *MCI:* data from 1093 subjects came from the Alzheimer's Disease Neuroimaging Initiative-1 (ADNI-1), ADNI-2 observational studies and the Investigation into Delay to Diagnosis of Alzheimer's disease with Exelon (InDDEx) clinical trial.
- **Endpoint:**
  - *Early stage PD:* Harmonized Part III score of the Movement Disorder Society Unified PD Rating Scale (MDS-UPDRS, or motor scores) (Ref. 1).
  - *MCI:* Clinical Dementia Rating–Sum of Boxes (CDR-SB).
- **Model:**
  - *Early stage PD:* Mixed-effects model to estimate and compare the endpoint rate of progression between subjects with a scan without evidence of DAT deficit (SWEDD) and those with DAT deficit (Ref. 1).
  - *MCI:* Mixed-effects beta regression model to estimate and compare the endpoint rate of progression between subjects with 'high' and 'low' ICV-HV values based on various cut-offs.
- **Enrichment:** Utility of biomarker enrichment was determined by various model outputs including statistical and clinical significance of the estimated covariate effect, and reduction in trial size by Monte Carlo simulations (Ref. 1).

## Results

- The selected base models to describe the progression of early stage PD and MCI are described in Table 1.
- Predictors of rate of progression in early stage PD and MCI are presented in Table 2.

**Table 1. Selected base models**

| Disease        | Model                             | Structure   |
|----------------|-----------------------------------|---|
| Early stage PD | Linear*1                          | $\frac{dScore_i}{dt} = r_i$   |
| MCI            | Generalized logistic (Richards)*2 | $\frac{dScore_i}{dt} = r_i \times Score_i \times \left[ 1 - \left( \frac{Score_i}{\max(Score_i)} \right)^\beta \right]$ |

\*1 Details are provided at Ref. 1.

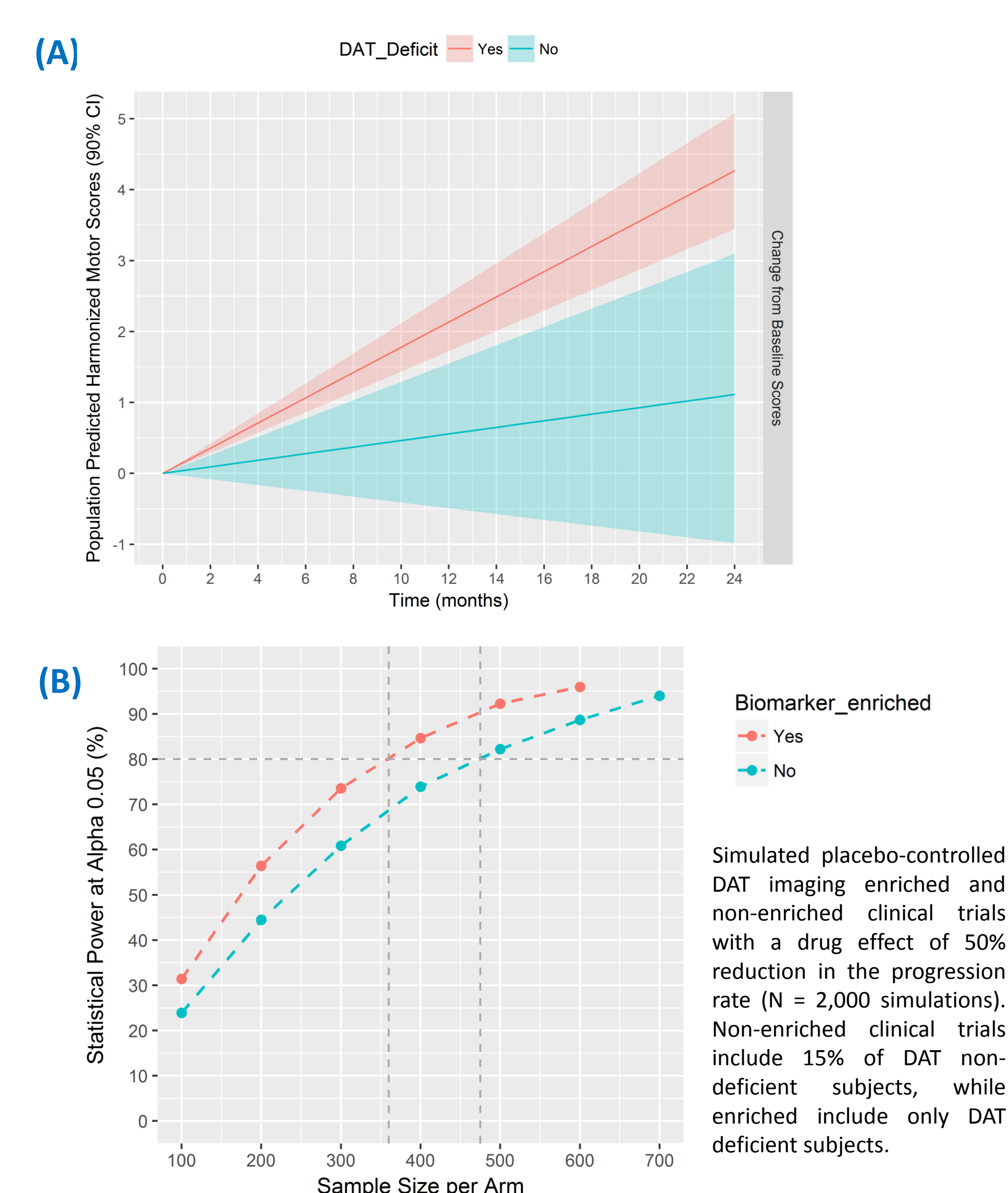
\*2 Details on the Richards model can be found at Ref. 4.

**Table 2. Predictors of rate of progression**

| Disease        | Rate Predictors                             |
|----------------|---|
| Early stage PD | DAT deficit status: yes or no               |
| MCI            | ICV-HV, age, gender, MMSE, APOE ε4 genotype |

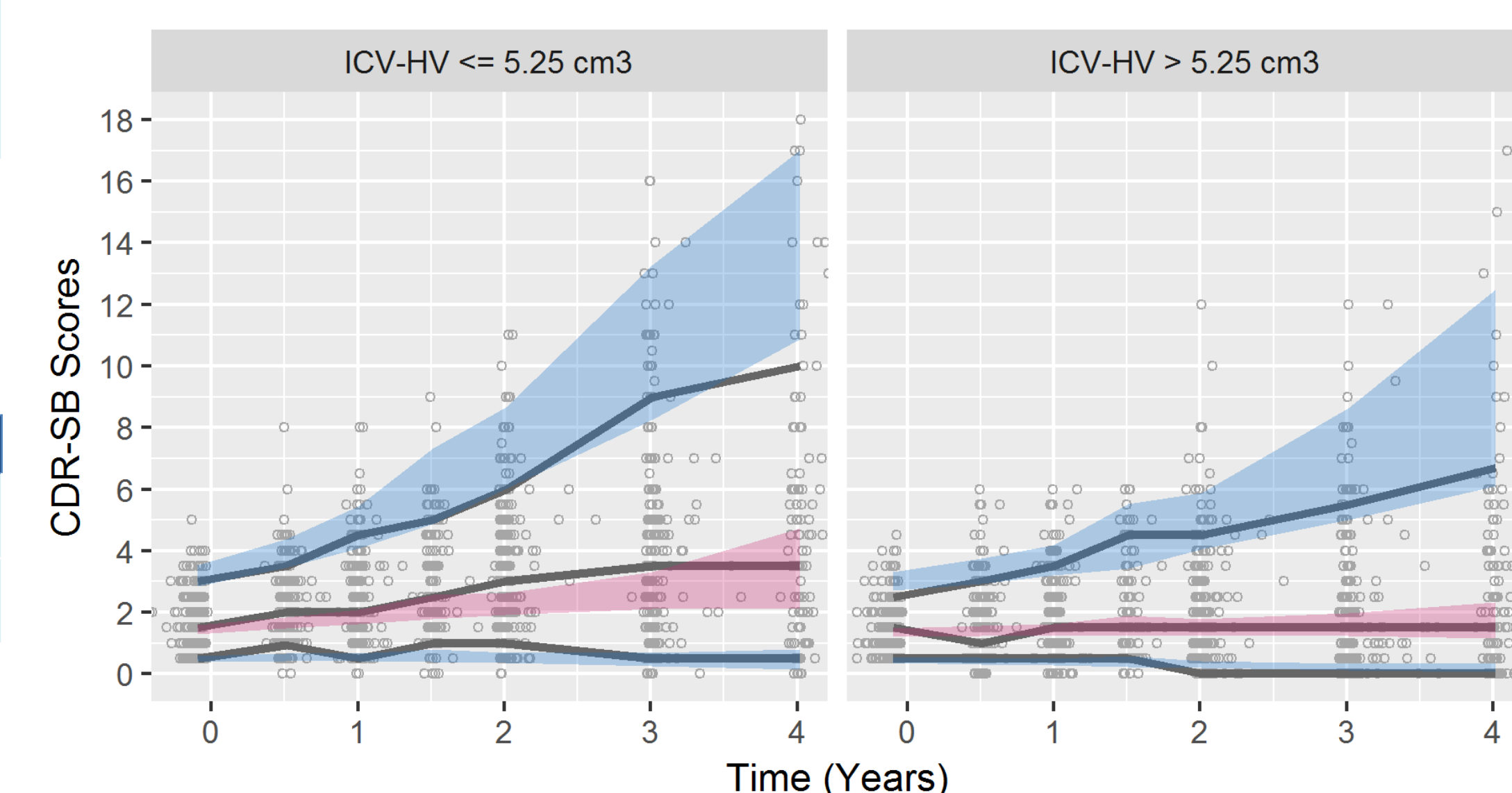
- **Early stage PD:**
  - Subjects with and without DAT deficit have an average monthly progression in scores of 0.18 (90%CI: 0.14, 0.21) and 0.05 (90%CI: -0.04, 0.13) point/month, respectively (Figure 2A; Ref. 1).
  - Under reasonable assumptions, a DAT-based enrichment strategy allowed a ~24% reduction of trial size to detect a drug effect of 50% reduction in progression rate with 80% probability at  $\alpha=0.05$  (Figure 2B; Ref. 1).

## Results (cont.)



**Figure 2. DAT imaging enrichment in early stage PD**

- **MCI:**
  - ICV-HV values ( $cm^3$ ) related to the rate of CDR-SB progression via a linear function, and the estimated effect was -0.884 (95% CI: -1.30, -0.47). This means that for each 1  $cm^3$  decrease in the ICV-HV, the progression rate increases by ~88% (Figure 3).
  - ICV-HV enrichment (inclusion of subjects with ICV-HV < 5.25  $cm^3$ ) allowed a sample size per arm of ~250 (vs. ~500 without enrichment) in a 2-year parallel study to detect a drug effect of 50% reduction in rate with 80% probability at  $\alpha=0.05$  (N=1600 Monte Carlo simulations).



**Figure 3. Visual predictive check stratified by ICV-HV.**

5.25  $cm^3$  is the median ICV-HV value of the dataset. Dropout has been included. One thousand simulations were performed. Open circles are observed scores; solid lines are the 10<sup>th</sup>, 50<sup>th</sup> and 90<sup>th</sup> percentiles of the observed scores; shaded areas are the 95% inter-percentile ranges of the simulations.

## Conclusions

- Model-informed analyses of potential enrichment biomarkers can streamline the pathway towards regulatory qualification, and improve clinical trial design efficiency.